The results are r ported in the table 5 from which it can be observed not only a peak of analgesic effect at two hours from the administration but also the superiority of the (d-d) isom r.

TABLE 5

Changes in pain threshold of inflamed and normal paws of rats receiving oral treatment with d-d Nxtio and d-l Nxtio

GROUP	TREATMENT	DOSE (mg/kg) p.o.	MEAN CHANGE IN PAIN THRESHOLD (0 +/- S.E.) FROM PRE-DOSE AT POST-DOSE TIME									
			1 HOUR		2 HOURS		4 HOURS					
			INFLAMED PAW	NORMAL PAW	INFLAMED PAW	NORMAL PAW	INFLAMED PAW	NORMAL PAW				
1	vehicle	-	-22.4 +/- 15.2	-40.5 +/- 17.8	-42.0 +/- 15.1	-52.6 +/- 1	-21.3 +/- 15.3	-39.2 +/- 13.9				
2	d-d Nxtio	6.25	-27.2 +/- 30.8	-12.8 +/- 17.8	-42.2 +/- 21.9	-17.7 +/- 1	-32.7 +/- 15.5	34.1 +/- 17.4				
3		12.5	32.6 +/- 40.1	-13.7 +/- 22.9	32.6 +/- 41.7	-23.4 +/- 1	30.9 +/- 40.8	10.7 +/- 23.7				
4		25	53.2 +/- 29.9	- 1.0 +/- 26.0	31.3 +/- 35.8	-33.5 +/- 2	41.9 +/- 35.3	18.7 +/- 35.9				
5		50	48.3 +/- 27.9	- 1.3 +/- 22.9	98.9 +/- 38.9	-38.8 +/- 1	79.4 +/- 42.7	25.7 +/- 24.3				
6	d-l Nxtio	6.25	-21.6 +/- 30.9	-14.3 +/- 20.0	-38.4 +/- 18.9	-24.5 +/- 2	-23.1 +/- 18.4	-10 +/- 25.5				
7		12.5	25.5 +/- 37.3	-15.4 +/- 28.8	20.5 +/- 38.7	-20.9 +/- 2	21.2 +/- 43.2	-12 +/- 15.8				
8		25	40.2 +/- 31.4	-10.8 +/- 27.5	23.2 +/- 34.6	-31.5 +/- 2	29.6 +/- 38.1	19 +/- 37.7				
9		50	42.3 +/- 31.8	- 1.4 +/- 10.3	60.2 +/- 45.7	-38.4 +/- 2	52.1 +/- 19.1	18 +/- 22.7				

At that point it is worth to note that the advantages achieved by the present invention must be evaluated as a function of the relevant advancement already achieved with the compounds of the European Patent 124.925 whereby the further improvement which is thus obtained is, in obviously relative terms, a result relevant as well and fully unforeseable.

Preliminary clinical investigations have been carried out, with the results hereinafter stated:

I. Gastric tolerability.

This investigation has been carried out at the University of Milan under the supervision of the professor Mauro Podda, and has been directed to evaluate the gastric tolerability of d-d Nxtio in comparison both with Naproxen and with the combination of Naproxen and thiopronine: the study has been carried out on 18

voluntary patients in the need of an analgesic and anti-inflammatory treatment.

The xperimental protocol was that of th double blind trial, the pati nts being randomly select d and treated for 10 days at a daily dosage of two tablets and mor particularly:

(i) for Nxtio tablets of 550 mg containing an amount of active compound corresponding to 337 mg of Naproxen;

(ii) for Naproxen, tablets of the drug named "Naprosyn" containing 500 mg of Naproxen;

(iii) for the patients treated with Naproxen + thiopronine, tablets were used having an overall weight of 550 mg and corresponding to 337 mg of Maproxen.

Each patient was subjected to endoscopy by optical fibers both before and after the treatment to assess the gastric tolerability.

According to the endoscopic results, in 3 patients (two treated with naproxen + thiopronine and one with naproxen only) antral erosion was observed, whereas in two patients treated with naproxen only the appearance of antral gastritis and a worsening of the duodenitis was respectively observed.

In only one patient treated with Nxtio a slight duodenal hyperemy was observed.

The conclusions drawn from the evaluation of the endoscopic oservations and from the analysis of possible undesirable side effects confirm that the compound of the invention is endowed with an optimum gastrointestinal tolerability.

II. Efficacy and tolerability of Nxtio in patients suffering from post-traumatic pain.

This investigation has been carried out under the supervision of the prof. E.Bottarelli of the Physiokinesitherapy Division of the Hospital G.Stuard of Parma (Italy).

50 voluntary patients suffering from algic symptomatology of post-traumatic origin have been treated according to an open type experimental protocol, in which Nxtio has been compared with Naproxen (as the drug sold on the Italian market as "Naprosyn").

Two tablets of Nxtio of the overall weight of 550 mg (corresponding to a content of Naproxen of 337 mg) and of Naprosyn (with a Naproxen content of 500 mg) were daily administered to the patients until the symptomatology disappeared but for no more than 7 days.

According to the results Nxtio has an optimum therapeutical efficacy against the pain and all clinical situations of traumatic origin; The very important feature assessed in this investigation is that by using Nxtio not only the patients recovered a satisfactory condition before the end of the treatment period, but that the action of Nxtio takes place earlier and in a more effective manner in comparison with that of the comparison drug (namely Naproxen). Of course this fact is very important when dealing with situations of acute symptomatology and moreover nothing in the prior art would suggest that this derivative of Naproxen would show such an activity (i.e.the analgesic one) and in a more favourable manner.

In this connection it is to be taken into account that in this investigation the patients were on the average about 70 years old, and thus more liable to side effects of gastrointestinal origin as induced from the treatment with an anti-inflammatory drug.

III.Efficacy and tolerability of Nxtio in patients with pre-menstrual syndrome.

This investigation has been carried out at the Endocrinology Division of the I.N.I. Institute of Grottaferrata (Rome - Italy) under the supervision of the Dr.Filippo Vita.

80 voluntary young women suffering from pre-menstrual syndrome have been treated with Nxtio in comparison with Naproxen ("Naprosyn") according to an open type experimental protocol.

The treatment has been carried out for 20 days, the patients being administered with 2 tablets per day.

According to the preliminary results Nxtio has a better therapeutical activity than the comparison drug.

IV.Efficacy and tolerability of Nxtio in patients affected from algic symptomatology of post-surgical origin.

This investigation is still in course at the Hospital of Legnano (Italy) under the supervision of the director.

The investigation has been carried out on 50 voluntary patients suffering from post-surgical pain, the patients being daily administered with two tablets of Nxtio or of Naprosyn according to an open type experimental protocol.

The administration period was dependent on the post-surgical behaviour of the patient, but never longer than 7 days.

From the analysis of the therapeutical results it has been assessed that Nxtio has a quicker and more

r levant efficacy than the comparison drug, accompanied by a v ry good tolerability, as confirmed by the lack of undesirabl side eff cts at the gastrointestinal level.

The pharmaceutical compositions according to the present invention comprise as the active ingredient the (d-d) diastereoisomer together with the standard vehicles and excipients.

In this connection reference is made to the disclosure of European Patent 124.925, which is here incorporated for reference.

The dosages of active principles shall be still those of the corresponding composition based on Naproxen whereby the therapeutical effect is obviously increased.

As a matter of fact in the clinical experiments being carried out the following unit dosages are used:

- Tablets and capsules with a content of 275 and 550 mg of Nxtio
- suppositories with the same unit dosages
- gel for topical treatment with a 10% b.w. content of active ingredient.

Claims

1. S-[d-2-(6-methoxy-2-naphthyl)propionyl]d-2-mercaptopropionamido acetic acid.

2. Use of the diastereoisomer of claim 1 for the treatment of the inflammatory states and as analgesic.

3. Pharmaceutical composition in form suitable for the administration by oral, topycal, rectal route, useful as anti-inflammatory and analgesic drug, characterized by containing as the active ingredient, the diastereoisomer of claim 1.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the Europ an Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number

EP 91100947.0

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,A	EP - B1 - 0 124 925 (FARMA RESA) * Totality * ----	1,3	C 07 C 327/32 A 61 K 31/265

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C 07 C 327/00
A 61 K 31/00

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 1+3

Claims searched incompletely: 2

Claims not searched

Reason for the limitation of the search:

Method for treatment of the human or animal body by therapy; Article 52 (4)

Place of search	Date of completion of the search	Examiner
VIENNA	15-04-1991	HOFBAUER

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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(57) Abstract

A pharmaceutical product for relief of the symptoms of angina pectoris and the like comprises an ester or a combination of an organic nitrate, and a salicylate, or derivative thereof, having anti-platelet activity.

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ESTER AND COMBINATIONS OF AN ORGANIC NITRATE AND A SALICYLATE

The invention relates to pharmaceutical products.

The term "organic nitrates" as used in this specification refers to pharmacologically active organic nitrate compounds which relieve, or act as prophylactic against, angina pectoris.

Organic nitrates are dilators of arterial and venous smooth muscle. The dilation action on the venous system increases the venous capacity allowing pooling of venous blood. This in turn reduces the volume of blood returning to the heart thereby lessening the strains on the heart muscle by reducing the pressure in the heart chambers (ventricles). This, in turn, reduces the oxygen requirements of the heart muscle. The dilation action on the arterial system is achieved by increasing the volume of the arterial system with consequent lower resistance to blood flow. This, in turn, reduces the work that the heart is required to do. In the coronary arteries (heart) a transient widening of the arteries (vasodilation) increases blood circulation to the heart muscle thereby increasing oxygen availability to the heart muscle.

Patients with coronary artery narrowing may suffer from angina pectoris which is usually brought on by exercise, motion or eating. The organic nitrates by virtue of their action described above relieve the symptoms of angina pectoris.

In more detail, organic nitrates act in two ways - indirectly and directly.

Indirectly: they are smooth muscle relaxants and thus dilate both arterial and venous blood vessels. At lower

doses their action is mainly on the venous system resulting in a decreased right and left ventricular filling pressure. At lower doses, however, they have little effect on the systemic (arterial) filling pressure. At higher doses, the arterial effects are more marked and decreased systemic resistance is accompanied by a reduction in blood pressure (Flaherty et al 1976). The venodilating and arterial effects of nitrates relieve ischaemia (the cause of angina, pain) by reducing determinates of myocardial oxygen demand.

Directly: they relieve ischaemia by direct action on the coronary vasculature thereby increasing intercoronary collateral flow and reversal of coronary artery spasm.

One widely used organic nitrate is isosorbide mononitrate (ISMN) which is an active metabolite of Isosorbide dinitrate (ISDN). ISMN has a high bioavailability and has a comparatively long half life (4-5 hours). Thus it is very suitable for prophylactic angina therapy. This is particularly so when it is presented as a sustained release formulation.

According to the invention there is provided a pharmaceutical product comprising:

an organic nitrate; and

a salicylate or a salt, ester, derivative, complex thereof, or salts of the ester, derivative or complex having anti-platelet activity.

In a particularly preferred embodiment of the invention, the pharmaceutical product is a salicylate ester of an esterifiable organic nitrate.

Preferably, the organic nitrate is directly esterifiable. In other words, the organic nitrate has an hydroxy group which is available for esterification.

The organic nitrate may be an isosorbide nitrate such as isosorbide 2-mononitrate or, most preferably isosorbide 5-mononitrate.

Alternatively, the organic nitrate is a glyceryl nitrate such as glyceryl trinitrate (also known as 1,2,3-Propanetriol trinitrate and Nitroglycerin).

Alternatively, the organic nitrate is a pentaerythritol nitrate such as pentaerythritol trinitrate (also known as Pentrinitrol).

Alternatively, the organic nitrate may be indirectly esterifiable by removal of a nitrate from the nitrate compound and replacement by an hydroxy group prior to esterification.

In this case, the organic nitrate may be selected from the group consisting of Erythritol Anhydride, Mannitol Hexanitrate, Trolnitrate Phosphate, Pentaerythritol Tetranitrate, Propatyl Nitrate, Clonitrate, and Isosorbide Dinitrate.

In a particularly preferred embodiment of the invention the product is formed by esterification of an esterifiable organic nitrate with acetylsalicylic acid.

The product may be adapted for oral administration or percutaneous administration.

The invention also provides a tablet or capsule comprising a pharmaceutical product of the invention.

The invention further provides a transdermal patch including a pharmaceutical product of the invention.

The invention especially preferably provides the compound Isosorbide 5-mononitrate-2-aspirinate.

In another aspect the invention provides a process for preparing a pharmaceutical product of the invention which comprises esterifying an esterifiable organic nitrate with acetylsalicylic acid.

Preferably, the esterification is carried out using a coupling reagent and/or a catalyst.

The coupling agent typically is a carbodiimide such as Dicyclohexylcarbodiimide (DCC).

The catalyst may comprise a pyridine derivative or paratoluene sulphonic acid.

Preferably, the esterification is carried out in non-aqueous conditions.

Typically, the process is carried out using methylenechloride as a solvent.

Preferably the process is carried out at a temperature below 5°C, most preferably at 0°C or below.

In another aspect of the invention the product is a combination product of the organic nitrate and the anti-platelet agent.

Preferably, the anti-platelet agent comprises acetylsalicylic acid.

In a preferred arrangement, the weight ratio of organic nitrate to acetylsalicylic acid is from 2:1 to 1:5, most preferably approximately 1:1.

The component products may be separated from each other in a single dose form. The barrier may be a physical barrier such as a membrane between the components. The membrane may be a coating of the components in microgranular or granular presentation. The coating may be on any or all of the components within the formulation.

Alternatively, the barrier is a chemical barrier.

Preferably, at least a portion of the organic nitrate is present in a slow release form.

Most preferably, the combination product comprises a capsule including the components.

The invention will be more clearly understood from the following description thereof given by way of example only.

EXAMPLE 1

Synthesis of acetylsalicyloxyisosorbide mononitrate

Materials:

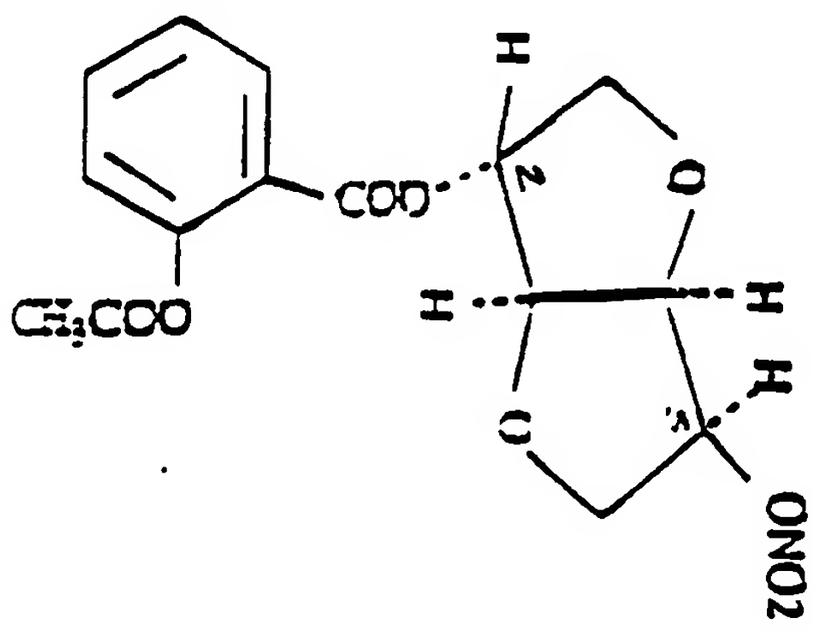
Acetylsalicylic acid
Isosorbide mononitrate
Dicyclohexylurea (DCC)
Dimethylaminopyridine (DMAP)

Dichloromethane (dry)
Citric acid solution (20%w/v in water)
Sodium bicarbonate aqueous solution saturated
Sodium sulphate anhydrous

Method:

Add DMAP (0.03 gm) and isosorbide mononitrate (1.85gm,0.01M) to a cold (0°C) and well stirred solution of acetylsalicylic acid (1.8gm, 0.01M) in dry dichloromethane (10ml). Gradually add DCC (2.06gm,0.01M). Stir for 10 minutes before removing the icebath and then stir for 3 hours at room temperature. Remove the precipitate by filtration. The filtered solution was washed with 2 x 25ml aliquots of cold 20% citric acid solution and then 2 x 25ml aliquots of saturated sodium bicarbonate solution. Dry the lower organic layer with anhydrous sodium sulphate filter and remove the solvent in vacuo. The product is purified on a sigel column using dichloromethane as eluent. The yield of the oily semisolid product was 50-75%.

The product has the following structure:



The product may be named as Isosorbide-5-mononitrate-2-aspirinate, or 2-{2-Acetoxybenzoyl}-isosorbide-5-

mononitrate, or 2-Acetylsalicyloxy-1,4:3,6-dianhydro-D-glucitol-5-nitrate.

Oil/low melting point solid Molecular formula $C_{15}H_{15}O_9N$
Molecular weight 353

Infra red spectrum (thin film) 1780,1740,1640 cm-1 The infra red analysis for isosorbide mononitrate is shown in Fig. 1. Fig. 2 is the infra red analysis for the product of the example.

Proton magnetic Resonance Spectrum See PMR BB-24 appended

Thin Layer Chromatogram: Sigel GF 254/dichloromethane rf=0.8

Mass spectrum (EI) MI 353

Because of the inherent lability of the starter and product ester groupings it is necessary to select mild reaction conditions. The general method of Neises, B and Steglich, W, Angew. Chem. Int Ed Eng. 17 (1978) No. 7, 522-524 was selected because of the mild reaction condition. The direct formation of acetylsalicyloxyisosorbide-5-mononitrate from acetylsalicylic acid and isosorbide - 5-mononitrate is accomplished by the use of the coupling reagent N,N1-dicyclohexylcarbodiimide (DCC). The particular virtue of this method lies in its suitability for acid sensitive substrates such as esters. The rate of reaction is greatly increased by addition of catalytic amounts of 4-dimethylaminopyridine. Pyridine or p-toluene sulphonic acid may also be used.

<u>Indirect Esterification</u>

Acid chlorides react with primary and secondary alcohols to give esters in good yield.

Anhydrides may also be used for the esterification of alcohols in the presence of a suitable catalyst. Acidic catalysts such as sulphuric acid or zinc chloride and basic catalysts such as pyridine are generally used.

Direct Esterification

Direct esterification procedures involving carboxylic acids and alcohols can be accomplished by the addition of concentrated sulphuric acid or dry HCl to the reaction mixture.

Various methods for the preparation of esters are described in "Comprehensive Organic Transformations" - A guide to functional group preparations by Richard C. Larock, VCH Publishers Inc 1989, especially pages 966-972, 978-979, 980-981, 985-987, 989-990.

As the product of Example 1 is an oil/low melting point solid, it is likely to be particularly suitable for percutaneous application, by means of a transdermal patch or for oral application in the form of a capsule, such as a soft gelatin capsule.

A widely used organic nitrate is Isosorbide Mono or di nitrate. Such agents act directly on the coronary arteries dilating them and thus improving the blood flow to the heart muscle and thus relieving the pain of angina pectoris. Another way that organic nitrates in general relieve the pain of angina is by reducing the requirements of the myocardium (heart muscle) for oxygen by reducing the volume of blood returning to the heart.

The pharmaceutical products of the invention are particularly for the prophylaxis of chronic stable angina pectoris. The invention provides a new combined prophylactic therapy which will deal with the pain of angina and decrease the risk of thrombosis leading to heart attack. Patients with angina pectoris have diseased coronary arteries. All patients with this degree of diseased coronary arteries are at increased risk of developing thrombosis (or clot).

In a particularly preferred embodiment of the invention the anti-platelet agent is ASPIRIN (acetylsalicylic acid).

Aspirin has been widely used for many years as an analgesic/anti-pyretic and anti-inflammatory agent. As such, it is a most useful drug. In more recent years, however, it has been discovered that aspirin has a powerful anti-platelet effect. Platelets are microscopic particles within the blood that, under certain circumstances, can stick together to form a thrombus (clot). Aspirin prevents the sticking together of platelets and thus helps prevent the occurrence of heart attack or its complications.

In the case of a two component product preferably the composition is in a form suitable for oral administration, typically in a tablet or capsule form.

The weight ratio of the nitrate to Aspirin may be from 2:1 to 1:5, most preferably 1:1.

In the case of a two component product the component products may be separated from one another in a single dose form. They may be separated by a barrier such as a

physical barrier provided between the components in a single capsule.

The component products may be separated from each other by a coating of gelatine or the like on one of the components, most preferably on the nitrate.

Alternatively, the barrier may be a chemical barrier, each of the components being present in a microgranulated form.

The composition may be arranged for any desired release profile. The components may be released simultaneously or in some cases the organic nitrate is released more slowly than the Aspirin.

The effect of the pharmaceutical product of the invention is in the treatment of angina pectoris and in reducing the risk of developing myocardial infarction.

It is anticipated that, while the invention has been specifically described with reference to the combination of Isosorbide nitrate and Aspirin, it is expected that combination products of other known anti-angina agents are anti-platelet agents may also be used in combination.

Providing a nitrate and an anti platelet agent in a single dose pharmaceutical product has considerable advantages from a compliance viewpoint. If a patient is required to take a nitrate and aspirin separately there is a risk that one or other will be forgotten. It is also quicker and easier for a doctor to prescribe such a combination product.

EXAMPLE 2

A capsule containing 8 mg of Aspirin, 15 mg of Isosorbide Mononitrate for immediate release and a slow release tablet containing 45 mg of Isosorbide Mononitrate.

A size 1 capsule was used. The ideal powder fill weight was in the region of 190 mg, containing 80 mg and 15 mg of Isosorbide Mononitrate respectively. The formulation for the powder fill was:

A.	Aspirin	80 mg
	ISMN	15 mg
	Microcrystallinecellulose	90 mg
	Talc	4 mg
	Magnesium Stearate	1 mg

A number of alternative formulations for a slow release tablet containing 45 mg of Isosorbide Mononitrate were made. The preferred formulation was:

B.	ISMN	45.0 mg
	Calcium H. Phosphate	30.0 mg
	Eudragit NE 40D	15.0 mg
	Magnesium Stearate	1.0 mg
	Water	q/s

The ISMN was blended with Calcium H. Phosphate and the resultant mix was granulated with Eudragit. The granules were sieved using a No. 10 sieve and dried at 40°C for 6 to 8 hours. Magnesium stearate and talc were added and the mixture was blended prior to compression.

Dissolution tests of the capsule incorporating A and B yielded a good longterm release profile which is plotted in Fig. 3.

EXAMPLE 3

Example 2 was repeated except that the granules of Example 2B were further blended with Eudragit RS/PO.

The results of dissolution tests are plotted in Fig. 4.

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

CLAIMS

1. A pharmaceutical product comprising:

an organic nitrate; and

a salicylate or a salt, ester, derivative, complex thereof, or salts of the ester, derivative or complex having anti-platelet activity.

2. A pharmaceutical product as claimed in claim 1 wherein the pharmaceutical product is a salicylate of an esterifiable organic nitrate.

3. A pharmaceutical product as claimed in claim 1 or 2 wherein the organic nitrate is indirectly esterifiable.

4. A pharmaceutical product as claimed in claim 1 or 2 wherein the organic nitrate is directly esterifiable.

5. A pharmaceutical product as claimed in claim 4 wherein the organic nitrate is an isosorbide nitrate.

6. A pharmaceutical product as claimed in claim 5 wherein the organic nitrate is isosorbide 5-mononitrate.

7. A pharmaceutical product as claimed in claim 5 wherein the organic nitrate is isosorbide 2-mononitrate.

8. A pharmaceutical product as claimed in claim 4 wherein the organic nitrate is a glyceryl nitrate.

9. A pharmaceutical product as claimed in claim 8 wherein the glyceryl nitrate is glyceryl trinitrate (1,2,3-Propanetriol trinitrate) (Nitroglycerin).

10. A pharmaceutical product as claimed in claim 4 wherein the organic nitrate is a pentaerythritol nitrate.

11. A pharmaceutical product as claimed in claim 10 wherein the pentaerythritol nitrate is pentaerythritol trinitrate (Pentrinitrol).

12. A pharmaceutical product as claimed in claim 3 wherein the organic nitrate is selected from the group consisting of Erythritol Anhydride, Mannitol Hexanitrate, Trolnitrate Phosphate, Pentaerythritol Tetranitrate, Propatyl Nitrate, Clonitrate, and Isosorbide Dinitrate.

13. A pharmaceutical product as claimed in any of claims 2 to 12 wherein the product is formed by esterification of an esterifiable organic nitrate with acetylsalicylic acid.

14. A pharmaceutical product as claimed in any preceding claim which is adapted for oral administration.

15. A pharmaceutical product as claimed in any of claims 1 to 13 which is adapted for percutaneous administration.

16. A tablet or capsule comprising a pharmaceutical product as claimed in any of claims 1 to 14.

17. A transdermal patch including a pharmaceutical product as claimed in any of claims 1 to 13 or 15.

18. Isosorbide 5-mononitrate-2-aspirinate.

19. A transdermal patch including isosorbide 5-mononitrate-2-aspirinate.

20. A soft capsule including isosorbide 5-mononitrate-2-aspirinate.

21. A process for preparing a pharmaceutical product as claimed in any of claims 2 to 20 which comprises esterifying an esterifiable organic nitrate with acetylsalicylic acid.

22. A process as claimed in claim 21 wherein the esterification is carried out using a coupling reagent.

23. A process as claimed in claim 21 or 22 wherein the esterification is carried out using a catalyst.

24. A process as claimed in claim 22 or 23 wherein the coupling agent is a carbodiimide.

25. A process as claimed in claims 23 or 24 wherein the catalyst is a pyridine derivative.

26. A process as claimed in claims 23 or 24 wherein the catalyst comprises paratoluene sulfonic acid.

27. A process as claimed in any of claims 21 to 26 wherein the esterification is carried out in non-aqueous conditions.

28. A process as claimed in claim 27 wherein the process is carried out using methylenechloride as a solvent.

29. A process as claimed in any of claims 21 to 28 wherein the process is carried out at a temperature below 5°C.

30. A process as claimed in any of claims 21 to 28 wherein the process is carried out at a temperature of 0°C or below.

31. A process substantially as hereinbefore described with reference to the Examples.

32. A pharmaceutical product whenever prepared by a process as claimed in any of claims 21 to 31.

33. A pharmaceutical product substantially as hereinbefore described with reference to the Examples.

34. A product as claimed in any of claims 1, 2 to 12, or 14 to 17 which is a combination product of the organic nitrate and the anti-platelet agent.

35. A product as claimed in claim 34 wherein the anti-platelet agent comprises acetylsalicylic acid.

36. A composition as claimed in claim 35 wherein the weight ratio of organic nitrate to acetylsalicylic acid is from 2:1 to 1:5.

37. A composition as claimed in claim 36 wherein the weight ratio is approximately 1:1.

38. A composition as claimed in claim 34 to claim 37 wh rein the component products are separated from each other in a single dose form.